INTELLECTUAL PROPERTY INDIA

सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

*I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application and Complete Specification filed in connection with Application for Patent No.**459/Del/02** dated **15th April 2002.***

Witness my hand this 28th Day of May 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1 0459-2

THE PATENTS ACT, 1970
(39 of 1970)

15 APR 2002

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A NOVEL METHOD OF STABILIZING BUPROPION HYDROCHLORIDE TABLETS"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. MANISH CHAWLA

b. RAJEEV S. RAGHUVANSHI

c. ASHOK RAMPAL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Group Leader – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 6343126; 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, MANISH CHAWLA, RAJEEV S. RAGHUVANSHI, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a. 15/04/02
(MANISH CHAWLA)

b.
(RAJEEV S. RAGHUVANSHI)

c.
(ASHOK RAMPAL)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 681009 dated **30.03.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 15TH day of **APRIL,** 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A NOVEL METHOD OF STABILIZING BUPROPION HYDROCHLORIDE TABLETS

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a novel method of stabilizing bupropion hydrochloride tablets, which also serves as an improved tabletting process for the preparation of sustained release bupropion hydrochloride tablets.

Bupropion hydrochloride is a well-known antidepressant and a non-nicotine aid to smoking cessation. GLAXOSMITHKLINE sells it in United States as WELLBUTRIN® (bupropion hydrochloride immediate release tablets), WELLBUTRIN® SR and ZYBAN® SR (bupropion hydrochloride sustained release tablets).

Bupropion hydrochloride is a water-soluble, crystalline solid, which is highly hygroscopic and susceptible to decomposition. Because of the drug's instability, the researchers working in this field have tried a number of different approaches to improve the storage stability of the drug in the formulation. US 5,358,970; US 5,763,493; US 5,731,000; US 5,427,798; US 5,968,553; US 5,541,231; and US 6,242,496 patents variously cover use of organic acids, carboxylic acids, dicarboxylic acids, inorganic acids, acid salts of an amino acids, sodium metabisulfite and sodium bisulfate as stabilizers for the bupropion compositions. Uses of acidic materials in pharmaceutical formulations require costly production procedures and equipment.

U.S. Pat. No. 5,427,798 describes formulations wherein drug release is achieved in a controlled manner by varying the surface area to volume ratio of the tablet. However, U.S. Pat. No. 5,427,798 relies on the inclusion of acids to stabilize the bupropion hydrochloride.

U.S. Pat. No. 6,306,436 discloses stabilized bupropion hydrochloride pharmaceutical compositions that are free of added acid and provide for sustained release of bupropion hydrochloride. Stabilization is achieved by particulate bupropion hydrochloride, which is coated with a membrane coating or by large size bupropion crystals. A drug particle coating is an expensive and time-consuming process.

Most of the prior art workers have used wet granulation method to prepare bupropion hydrochloride immediate release or sustained release tablets.

U.S. Pat. No. 6,238,697 describes methods and formulations for making extended release bupropion hydrochloride tablets using direct compression method, and tablets formed thereby, are provided which combine bupropion hydrochloride, binders, fillers, glidants and lubricants under low shear conditions to form hard, chip-resistant tablets which exhibit improved cohesiveness and are easily and reproducibly formed without adhering to the compression punches. The invention employs use of sodium sulfite or potassium metabisulfite to improve the stability of bupropion hydrochloride.

Direct compression requires use of specific excipients of particular size and density to avoid segregation and content non-uniformity problems. Use of specific particle size and density range excipients add to cost and make the process tedious. Moreover, the success of direct compression process depends on bulk density, tap density and particle size distribution of the drug.

Wet granulation provides better content uniformity, but is not advisable for active ingredients like bupropion hydrochloride, which are hygroscopic and susceptible to decomposition. Moreover, polymers, especially hydrophilic polymers usually used in achieving extended release, interact with the aqueous system making wet granulation a cumbersome process. The wet granulation process with hydrophilic polymers may also result in variable release characteristics depending on the degree of hydration of the polymer. Even the fluid volume of the granulating agent and granulation time may also affect the release characteristics. Use of the organic solvent lead to the problem of residual solvents and extra cost for maintaining the environmental standards both inside the plant and outside surroundings.

Hence, there is a need, not only for a better stabilization method but also for an improved tabletting process.

Inventors of the present invention have discovered that bupropion hydrochloride tablets can be stabilized by dry granulation process without having to add any stabilizer. Dry granulation also serves as an improved tabletting process for the preparation of sustained release bupropion hydrochloride tablets. Therefore the method of the invention not only provides the stabilization of bupropion hydrochloride without having to use an acid stabilizer or coated bupropion hydrochloride particles or bigger size bupropion

hydrochloride crystals as used by the prior art researchers, but also provides a better tabletting process for the preparation of sustained release tablets.

Therefore, the primary object of the invention is to provide a novel method of stabilizing bupropion hydrochloride tablets by a dry granulation process, wherein the tablet contains at least about 80% of undegraded bupropion hydrochloride after storage for two months at 40°C and 75% relative humidity.

Another object of the invention is to provide an improved tabletting process for the preparation of sustained release bupropion hydrochloride tablets.

The dry granulation process of the present invention comprises the steps of:

a) blending bupropion hydrochloride and other pharmaceutically acceptable excipient(s),

b) compacting or slugging,

c) sizing the compacted / slugged material of step (b) into granules,

d) Compressing the granules to form tablets.

The method of the invention is simple and produces tablets having good stability on storage and desired sustained release characteristics.

The method avoids the use of an acid stabilizer or coated bupropion hydrochloride particles or bigger size bupropion hydrochloride crystals, thereby resulting in reduced cost.

It also precludes the use of organic solvent during wet granulation. Therefore, the problem of residual solvent is automatically eliminated.

Moreover it eliminates the variability in the degree of hydration of hydrophilic polymers and its consequent effect on release characteristics.

The process provides granules with consistent hardness and increased density. Granules for high-speed tabletting or encapsulation are produced with reproducible granule size distribution. Less variation in particle size distribution reduces the need for reprocessing fines.

The process has good reprocessing potential as the compacts / slugs / tablets could be crushed into powder and re-compacted to make the tablets without affecting drug release profiles.

Therefore, the present invention provides a method for producing bupropion hydrochloride tablets that are stable on storage and have desired sustained release characteristics.

For the purpose of the present invention the term "bupropion hydrochloride" refers to the hydrochloride salt of m-chloro-α-(t-butylamino)propiophenone.

The pharmaceutically acceptable excipients of the invention may be selected from amongst the release rate controlling polymers, diluents, binders, lubricants, glidants and coloring agents which are compatible with bupropion and which would help in optimizing tablet robustness and drug dissolution from the tablet.

For the present invention, release rate-controlling polymers may be selected from any such pharmaceutically acceptable excipients, which can control the rate of release of the active ingredient. Preferably such release rate-controlling polymers can be selected from the group consisting of cellulose derivatives, acrylates, Polyvinlyacetate / Povidone mixture, polyethylene oxides, starch and their derivatives, gums, alginates, carbohydrate based polymers, polysaccharides or combinations thereof.

Cellulose derivative can be selected from the group consisting of ethyl cellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose and sodium carboxymethylcellulose of different degree of substitution and molecular weights. These release rate-controlling polymers can be used alone or in combination. Various degrees of substitution and / or different molecular weights corresponding to a different degree of viscosity can be used as suitable cellulose based rate-controlling polymers.

The term "Acrylates" is used to describe linear, non-crosslinked copolymers that contain combinations of acrylic acid, methacrylic acid and their simple esters. Acrylates can be selected from the group consisting of carbomer, polycarbophil and EUDRAGIT®.

The name "Carbomer" is used to describe high molecular weight cross-linked homopolymers of acrylic acid. Carbomers commercially available under the trademark Carbopol® may be selected from Carbopol® -934P, 971P or 974P.

Methacrylic acid polymers and copolymers commercially available under the trademark EUDRAGIT® s are particularly preferred.

Rate controlling polymer can be used in a concentration of 5% to 60% of the tablet weight depending on the polymer used. The use of hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose, Polyvinlyacetate / Povidone mixture or Carbopol® -971P is preferred. These polymers swell to form a hydrophilic matrix system, which control the release of bupropion hydrochloride. The tablet hydrates on wetting with aqueous fluids and hydrophilic polymers form a gel layer. Due to permeation of aqueous fluid into the tablet the thickness of gel layer is increased, and bupropion hydrochloride diffuses slowly out of the gel layer. Slow erosion of the swollen gel may also contribute to drug release.

Diluents of this invention may be selected from any such pharmaceutically acceptable excipient, which gives bulk to the composition and improves compressibility. Preferably those diluents may be selected from starch, microcrystalline cellulose, lactose, glucose, mannitol, alginates, alkali earth metal salts, dicalcium phosphate, glyceryl monostearate or polyethylene glycols. Microcrystalline cellulose is particularly preferred.

Binders of this invention may be selected from any such pharmaceutically acceptable excipient, which has cohesive properties to act as a binder. Preferably those excipients are starch, gelatin, highly dispersed silica, mannitol, lactose, polyethylene glycol, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose and natural or synthetic gums.

Lubricants of the present invention may be selected from talc, stearic acid, magnesium stearate, other alkali earth metal stearate like calcium, zinc etc., sodium lauryl sulphate, hydrogenated vegetable oil, sodium benzoate, sodium stearyl fumarate, glyceryl monostearate and PEG 4000.

Glidants of the present invention may be selected from colloidal silicon dioxide and talc.

The ingredients are blended and the blend is compacted by roller compaction. The compactor can have rollers and powder transport screws of different designs. Alternatively, this blend could be compressed to make slugs. For the purpose of the present invention compaction or slugging, could be done of either bupropion alone or with rate controlling polymer and/or with excipient(s).

The compacted / slugged material is sized by a suitable machine like oscillating granulator / Multimill / Fitzmill and sieved into the desired granule size.

As an optional step, the granules that are either too large or too small are recycled and combined with original powder mix and passed through the roller compactor or tabletting machine. Normally 30-70% of coarse granules (retained on 44-mesh sieve & passed through 18- mesh sieve) are preferred and are usually achieved in a single compaction cycle.

These granules are optionally lubricated with the lubricant and are compressed to form tablets. Optionally these granules can be capsulated into the hard gelatin capsules.

These tablets may be given a coating to enhance the aesthetic appeal.

The present invention is further illustrative by, but is by no-means limited to, the following examples.

EXAMPLES 1 - 4: Bupropion hydrochloride 150-mg formulations

Ingredient	Weight (mg) per tablet			
	Example 1	Example 2	Example 3	Example 4
Bupropion hydrochloride	150.00	150.00	150.00	150.00
Hydroxypropyl cellulose –M	63.00	-	-	31.5
Polyvinlyacetate/ Povidone mixture	-	63.00	-	-
Carbopol® 971P	-	-	63.00	31.5
Microcrystalline cellulose	200.00	200.00	200.00	200.00
Stearic acid	3.2	3.2	3.2	3.2
Total	416.00	416.00	416.00	416.00

The above bupropion hydrochloride formulations were prepared using the following process:

1. Bupropion Hydrochloride, Microcrystalline cellulose and rate controlling polymers are sifted through 44 BSS sieve and lubricated with stearic acid (half quantity).
2. Blend of step 1 is compacted using a roller compacter.
3. Compacts are sized through oscillating granulator and sifted through 18 BSS sieve.
4. Fines obtained are recycled to achieve the desired ratio of coarse and fines.
5. Granules of step 4 are lubricated with remaining quantity of stearic acid and compressed into tablets.

The stability of the tablets prepared as per the composition and process of Examples 1 -4 at 40 °C/ 75% RH is given in Table-1.

Table 1: Comparative stability of Bupropion hydrochloride tablets prepared as per the composition of Examples-1 -4 vs Commercially available bupropion hydrochloride tablets (WELLBUTRIN SR ® tablets).

Stability conditions	% bupropion hydrochloride				
	EXAMPLES				WELLBUTRIN SR ®
	1	2	3	4	
Initial	98.5	96	102	101.8	105.3
1 month at 40°C / 75% RH	97.0	95	101.3	-	95.1
2 month at 40°C / 75% RH	93.6	90.0	102.4	104.5	89.0

RH = Relative Humidity

* of added quantity

The dissolution profile of the tablets prepared as per the composition and process of Examples 1, 3, 4 is given in Table-2.

TABLE-2 DISSOLUTION PROFILES OF BUPROPION HYDROCHLORIDE (150 mg) FORMULATIONS (in distilled water 900ml at 50 rpm using USP-2 apparatus).

Time (hrs)	% bupropion hydrochloride dissolved		
	Example1	Example 3	Example 4
0.5	22	19	20
1	34	26	29
2	48	37	41
4	64	53	59
6	73	67	69
8	78	72	72

The above data clearly indicates that method of the present invention stabilizes bupropion hydrochloride tablets without any stabilizer and also serves as an improved tabletting process for the preparation of sustained release bupropion hydrochloride tablets.

WE CLAIM:

1. A method of stabilizing bupropion hydrochloride tablets by a dry granulation process.

2. The method according to claim 1 wherein dry granulation is used as an improved tabletting process for the preparation of sustained release bupropion hydrochloride tablets.

3. The method according to claim 1 or 2 wherein the tablet contains at least about 80% of undegraded bupropion hydrochloride after storage for two months at 40°C and 75% relative humidity.

4. The method according to claim 1 or 2 wherein the dry granulation process comprises the steps of:

a) blending bupropion hydrochloride and other pharmaceutically acceptable excipient(s),
b) compacting or slugging ,
c) sizing the compacted / slugged material of step (b) into granules ,
d) compressing the granules to form tablets.

5. The method according to claim 4 wherein the step (b) is carried out by compaction.

6. The method according to claim 5 wherein the compaction is done with roller compactor.

7. The method according to claim 4 wherein the step (c) is carried out by milling.

8. The method according to claim 4 wherein the granules of step (c) are lubricated before compression.

9. The method according to claim 4 wherein the tablet is coated after compression.

10. The method according to claim 4 wherein the other pharmaceutically acceptable excipients comprises release rate controlling polymer(s), diluents, binders, lubricants, glidants and coloring agents.

11. The method according to claim 10 wherein the release rate controlling polymers may be selected from the group consisting of cellulose derivatives, acrylates, Polyvinlyacetate / Povidone mixture, polyethylene oxides, starch & their derivatives, gums, alginates, carbohydrate based polymers, polysaccharide or combinations thereof.

12. The method according to claim 11 wherein the cellulose derivative is selected from the group consisting of ethyl cellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose or a mixture thereof.

13. The method according to claim 12 wherein the cellulose derivative is hydroxypropyl cellulose.

14. The method according to claim 11 wherein the acrylate is carbomer, polycarbophil or EUDRAGIT®.

15. The method according to claim 14 wherein carbomer is selected from Carbopol® -971 P, 974 P and 934 P.

16. The method according to claim 10 wherein the diluent is microcrystalline cellulose.

17. The method according to claim 10 wherein the lubricant is stearic acid.

18. A method of stabilizing bupropion hydrochloride sustained release tablets substantially as described and illustrated by the examples herein.

Dated this **15TH** day of **April, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary